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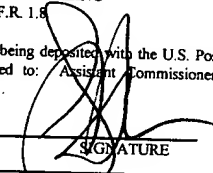
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RE: *USSN 07/431,533 for "URINARY TUMOR ASSOCIATED ANTIGEN,
ANTIGENIC SUBUNITS AND METHODS OF DETECTION" by Donald Morton
et al. (Attorney Dkt No.: CADL:002/HYL)*

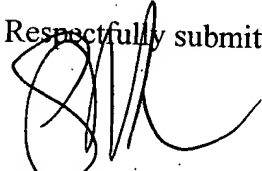
Sir:

Enclosed for filing in the above-referenced patent application is:

- (1) An Appeal Brief (in triplicate) with enclosed appendices 1 and 2 and exhibit A-J;
- (2) A check in the amount of \$150.00 as the fee for the Appeal Brief; and
- (3) A return postcard to acknowledge receipt of these materials. Please date stamp and mail this postcard.

A fee as set forth in 37 C.F.R. §§ 1.16-1.21 in the amount of \$150.00 is enclosed herewith. If an appropriate check has not been enclosed, or if it is insufficient under 37 C.F.R. §§ 1.16 to 1.21, the Commissioner is hereby authorized to deduct any necessary fees from Fulbright & Jaworski Deposit Account No. 50-1212/CADL:002/HYL.

Respectfully submitted,



Steven L. Highlander
Registration No. 37,642

encl.

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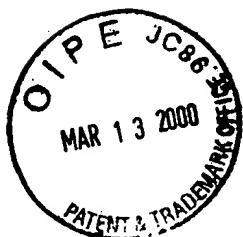


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I. REAL PARTIES IN INTEREST

The real parties in interest are the inventors, Drs. Rishab Gupta, Dr. David Euhus, and Dr. Donald Morton.

II. RELATED APPEALS AND INTERFERENCES

There are no interferences or appeals for related cases.

III. STATUS OF THE CLAIMS

Claims 1-46 were filed with the original application. Claims 47-79 were added during prosecution. Claims 1-18, 20-61, 67, 68 and 71 have been canceled. Thus, claims 19, 62-66, 69, 70 and 72-79 are pending and stand appeal. A copy of the appealed claims is attached as APPENDIX 1 to this brief.

IV. STATUS OF AMENDMENTS

No amendments have been filed following issuance of the final Office Action.

V. SUMMARY OF THE INVENTION

The present invention is drawn to compositions and methods relating to Urinary Tumor Associated Antigen, or "UTAA." This high molecular weight glycoprotein was initially detected in the urine of melanoma patients, but later found to occur in other bodily fluids. Specification at page 13, lines 6-10. The UTAA has been purified away from other proteins and used to make a monoclonal antibody specific for UTAA. Specification at pages 13-14. Further characterization reveals a polypeptide subunit of 90-100 kD, with a complexed weight of 590-620 kD under non-

reducing conditions. The isoelectric point is 6.1. Specification at page 15, lines 2-17. Also provided are methods for using UTAA to induce or enhance immune response in subjects. Specification at page 16, lines 27-30.

VI. ISSUES ON APPEAL

- A. Are claims 19, 62-66, 69, 70 and 72-79 properly rejected under the doctrine of obviousness-type double-patenting over the claims of U.S. Serial No. 08/462,570?
- B. Are claims 19, 62-66, 69, 70 and 72-79 obvious over Euhus *et al.* (Exhibit A); in view of Exley (Exhibit B), Rote *et al.* (Exhibit C) or Finck *et al.* (Exhibit D); and Pharmacia (Exhibit E), Ljungquist (Exhibit F) and Goldenberg (Exhibit G)?¹

VII. GROUPING OF THE CLAIMS

Claims 63, 64, 66, 69 and 70 stand or fall separately from the other claims with regard to the §103 rejection over Euhus and its supporting references. As explained in detail in the Argument, these claims recite particular levels of purity that are not enabled, taught or even suggested by the cited references.

VIII. SUMMARY OF THE ARGUMENT

The examiner continues to maintain the rejection of all claims over Euhus in view of a variety of references. Throughout this prosecution, it has been appellants' position that Euhus cannot be considered enabling for Urinary Tumor Associated Antigen (UTAA). Appellants have pointed out why one would have to, in essence, recreate the invention from scratch with only Euhus and the supporting references to rely upon. Even if one would have been able to, *de novo*, recreate the invention, one would not have been able to confirm that the isolated protein was the same as the one described by Euhus.

The examiner has steadfastly maintained, despite these arguments, that Euhus does provide an enabling disclosure. To further support their position, appellants have provided *three* expert declarations, each of which conclude that Euhus, in fact, contained insufficient information for the skilled artisan to produce purified UTAA. This showing was persuasive enough to actually overcome a rejection based on Euhus alone, but the examiner has resurrected the rejection in light of various secondary references.

However, none of the secondary references can correct the defects in Euhus, as Euhus is the only reference that substantively addresses UTAA. The secondary references, instead, provide isolated and generalized disclosures that might only be relevant if Euhus provided sufficient information to allow the purification of UTAA and an unambiguous definition of its structure. Since neither Euhus nor any of the other references can point to such a teaching, it again is submitted that the rejection is improper.

IX. ARGUMENT

A. *The Rejection for Obviousness-Type Double-Patenting²*

The examiner has raised a new rejection of all pending claims over claims 14-17 and 48-60 of U.S. Serial No. 08/462,570 for obviousness-type double-patenting. Appellants traverse the rejection but, in the interest of advancing the appeal, provide the attached terminal disclaimer, thereby obviating the rejection.

¹ The final Office Action actually indicates that only claims 62-66, 69, 70 and 73 are rejected under §103. Clarification is requested.

² This rejection has been styled as a “§101” rejection. However, the entire discussion relates to obviousness-type double-patenting, not “same invention” double-patenting. Thus, the rejection is addressed as an obviousness-type double-patenting situation.

B. The Rejection Under 35 U.S.C. §103

The examiner maintains the rejection, under §103, over Euhus *et al.* (Exhibit A); in view of Exley (Exhibit B), Rote *et al.* (Exhibit C) or Finck *et al.* (Exhibit D); Pharmacia (Exhibit E), Ljungquist (Exhibit F) and Goldenberg (Exhibit G). The examiner alleges that, though Euhus does not anticipate the claims, its teachings, when combined with various secondary references, obviate all of the pending claims. Appellants respectfully traverse.

Euhus is cited as disclosing UTAA and methods for its isolation. Rote is said to teach identification of tumor-associated antigens detected by autologous sera in the urine of patients with solid neoplasms. The antigens are said to be heat stable at 100°C for 60 min., and have a molecular weight of 10⁶ daltons, which dissociates into smaller subunits by treatment with 6M urea. Finck is said to teach tumor-associated antigens in the urine of patients with colon carcinoma. The antigens are larger than 10⁶ daltons and heat stable at 100°C. The Pharmacia reference is cited for gel filtration techniques. Ljunquist is said to teach purification of endonuclease IV by a combination of ammonium sulfate, gel filtration, heat and DNA-cellulose chromatography. Goldenberg teaches the production of antibodies to CEA.

At the outset, the rejection is traversed on the same basis as argued in the previous responses and the earlier brief - that the Euhus reference is not enabling. As discussed extensively on the record, the teachings of Euhus are not sufficient to permit one to reproducibly make and use the invention. It is well established that a reference must teach how to make and use the claimed invention, *i.e.*, must “enable” the claimed invention, for it to be a *valid* reference against the claims

of an application. In *Paperless Accounting Inc. v. Bay Area Rapid Transit Sys.*, 231 U.S.P.Q. 649 (Fed. Cir. 1986), the PTO's reviewing court said that a “§102(b) reference ‘must sufficiently describe the claimed invention to have placed the public in possession of it’ ‘[E]ven if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it was not enabling.’”

The examiner's arguments to the contrary merely highlight that the reference, at best, provide an invitation to one of skill in the art to *try* to reproduce the invention while sifting through a variety of technologic parameters that may or may not result in obtaining of a purified antigen composition comprising UTAA. “Obvious to try” is not the standard for obviousness, however, and the present evidence already shows why this rejection is improper. *In re O'Farrell*, 7 USPQ2d 1673 (Fed. Cir. 1988). However, appellants will once again delve into the specifics of the rejection and why it is improper.

1. Parameters Necessary for the Isolation of UTAA from Urine

The examiner argues that the Pharmacia reference teaches how to isolate proteins using ion exchange and gel filtration. This is not contested. The examiner also provides an extensive discussion of how one could use autologous sera to find such antigens once they had been fractionated. However, this clearly is a circular argument and is an essential flaw in the examiner's reasoning. Assuming one could isolate *some* fraction containing UTAA, how would one know that they had purified the correct antigen *or* the correct antibodies, much less identify a patient that even contained these substances? The answer, of course, is that they could not know since the prior art

fraction containing MW size. 110 kDa

fails to teach which fraction contained UTAA, or how one could identify UTAA from any other protein using any readily obtainable, well-characterized antibodies.

Thus, what the examiner is proposing is that the skilled artisan go back to “square one” and repeat appellants’ invention without any significant assistance from the cited art. Whether or not they would achieve the same result, *i.e.*, the claimed invention, is entirely up to chance -- chance that the skilled artisan would select the proper parameters for purification, chance that the skilled artisan would select the proper starting materials, and chance that the skilled artisan would pick the appropriate purified fraction (by either guessing, or by using an antibody source which itself would be selected on the basis of chance). In sum, the examiner’s proposal is nothing but a recitation of serendipity that is devoid of the ***likelihood of success*** that is required for legal obviousness. *In re O’Farrell*.

2. Structure and Immunologic Profile of UTAA

The examiner also argues that proteins can be isolated without knowledge of their amino acid sequence. In addition, it is argued that the present disclosure, with respect to UTAA structure, is the same as that presented in the Euhus reference. Finally, it is argued that antibodies to UTAA are “known,” and hence, their disclosure “is not any different from that of the claimed monoclonal antibody against the claimed UTAA.”

While it is true that there is no disclosure of an amino acid sequence, the present application contains considerably more information with regard to how one goes about purifying UTAA specifically, not how one goes about purifying proteins generally. Thus, the fact that there is no

sequence is not problematic from an enablement standpoint. By following the teachings in the instant specification, one can, without any doubt, isolate highly pure UTAA.

On the other hand, the cited prior art is nothing more than an acknowledgement that something called UTAA exists, along with a collection of general techniques that *might* purify UTAA, without any indication of how to confirm this or to identify which fraction actually contains UTAA. Thus, there is a major difference in the enabling quality of the present specification and the Euhus reference.

As to the equivalence of the disclosed monoclonal antibody and patient serum, assuming that this is true, appellants again ask how one could determine that a given serum, chosen by the skilled artisan, would bind to UTAA as opposed to some other antigen? Again, the answer is that one would *not* know. To the contrary, the skilled artisan could use the antibody disclosed in the present application, AD1-4OF4. Its unique ability to identify UTAA is another substantial difference between the present specification and Euhus. If the examiner believes it would advance the prosecution, appellants would be willing to deposit the antibody with a Budapest Treaty authorized depository.

3. The Reisfeld Declarations

In previous responses, appellants provided the examiner with two declarations (Exhibits H and I) from Dr. Ralph Reisfeld, Head of the Division of Tumor Biology at the Scripps Research Institute. In his first declaration, Dr. Reisfeld opined that one of skill in the art, upon reading the Euhus abstract, could not expect to reproduce the invention given the scant teachings provided

therein. In particular, it was argued that the skilled artisan would not know the key conditions (ionic strength, pH, retention times) under which a successful isolation was to be performed:

3. Although it is true that the Euhus abstract describes an antigen designated U-TAA, which is the subject matter of the instant claims, the abstract does not enable the isolation and purification of U-TAA, since it clearly lacks the information necessary to accomplish this task. Specifically, the Euhus abstract only identifies U-TAA as existing in IgG and IgM fractions in the serum of some melanoma patients, provides its molecular mass and the fact that it contains at least four subunits of varying molecular mass. It does not, however, provide any information on the details or operating parameters of U-TAA isolation. Key conditions such as the proper pH or ionic strength under which isolation was conducted are missing, as are the migration distances or retention times for gel or column purification. Without this information, the Euhus abstract definitely lacks the necessary, detailed information to reproducibly isolate and purify U-TAA. Without such detailed information, the antigenic compositions set forth in the instant claims could not be predictably generated.

4. Therefore, based on my 40 years of experience in the isolation, purification and characterization of biological products similar to U-TAA, those of skill in the art would not have held a reasonable expectation of success in reproducing the work described in the Euhus abstract, based solely on that disclosure.

Reisfeld Declaration I (Exhibit H). Still, the examiner maintained the rejection.

In his second declaration, Dr. Reisfeld noted that the abstract also contained no information on the sequence or immunogenic identity of the claimed antigen and, thus, even if it could be isolated, the skilled artisan would not know that the antigen was the same as that claimed. Thus, based on his extensive experience, Dr. Reisfeld found the Euhus disclosure as lacking a teaching sufficient to permit one of skill in the art to repeat the claimed invention:

3. The Euhus abstract merely relates to an antigen designated U-TAA. Yet, the abstract does not provide any information that would permit those of skill in the art to confirm that a given antigen, if isolated, was or was not the U-TAA of the abstract. Specifically, the Euhus abstract only identifies U-TAA as existing in IgG and IgM fractions in the serum of some melanoma patients, provides its predicted molecular mass and asserts that the antigen contains at least four subunits of varying molecular mass. It does not, however, provide any information on the amino acid sequence of this molecule.

Thus, a meaningful description of this molecule is not provided by the abstract. Without such information, those of skill in the art would not know if they had isolated what Euhus *et al.* had designated as U-TAA.

4. Similarly, the Euhus *et al.* abstract is devoid of any information regarding the immunologic identity of the antigen. Though a murine antibody that binds U-TAA is mentioned, this antibody is neither described nor was it publicly available at the time the instant application was filed. Moreover, the method by which the murine antibody was produced (*e.g.* antigen composition, immunization regimen, selection criteria) is not described. Without such information, those of skill in the art would not have had the Euhus antibody, much less been able to use it to determine if they had isolated what Euhus *et al.* had designated as U-TAA.

Reisfeld Declaration II (Exhibit I). In conclusion, Dr. Reisfeld reiterated that, “based on my 40 years of experience ..., reproduction of the work described in the Euhus *et al.* abstract would have relied, almost entirely, on an empirical “trial and error” approach, and thus would have lacked any reasonable and reliable expectation of success from [it’s] inception. Even if those of skill in the art would have fortuitously reproduced the work described in the Euhus *et al.* abstract, they could not have confirmed such a success with the information available.”

In appellants’ first brief, these same arguments were advanced with success over the then pending obviousness rejection. It is unclear why the examiner now believes that the citation of additional references, none of which address the issues raised by Dr. Reisfeld, undercut appellants’ position. It remains only to note that the same rationale that struck down the rejection of Euhus *et al.* alone applies to the present rejection.

4. The Shively Declaration

Rather than accepting these declarations, the examiner continues to improperly substitute her own opinion for that of the expert declarant. However, in an effort to advance the prosecution, appellants offered yet another declaration (Exhibit J), this one from Dr. John

Shively, Chairman of Immunology at the Beckman Research Institute, City of Hope. Therein, Dr. Shively explains that the Euhus abstract "does not contain sufficient information to enable purification of UTAA." This opinion was based on the facts that (i) the abstract describes the purification of antigen antibody complexes that contained numerous other species, and (ii) there was insufficient information on how to purify UTAA from this heterogeneous composition. Further, Dr. Shively notes that only in later, post-published papers, were the specific parameters necessary for purification of UTAA finally spelled out:

3. As an expert in the field, I believe that the Euhus abstract does not contain sufficient information to enable purification of UTAA. Furthermore, based on a comparison of this abstract and subsequent articles (Euhus *et al.*, *Int. J. Cancer*, 45:1065-1070, 1990, and Euhus *et al.*, *Cancer Immunol. Immunother.*, 32:214-220, 1990), it is my opinion that the antigen as described in the abstract was not purified to homogeneity, nor characterized sufficiently to allow even an expert to positively identify the same antigen. This opinion is based on the stated fact in the abstract that UTAA was usually isolated as an antigen-antibody complex in a fraction containing other antibody complexes. Such an unfractionated complex must contain many other antibodies and proteins irrelevant to UTAA and its cognate antibodies. They also state that some sera were free of immune complexes, but insufficient information was given on how to identify such sera, or how to modify the isolation procedure to successfully isolate the antigen under these distinct circumstances. In subsequent articles (cited above), the authors describe further purification steps and primary evidence (Coomassie Blue stained gels and Western blots) that convincingly establish a method of purification, the purity and the molecular mass of UTAA.

4. While the examiner is correct that molecular masses reported from SDS gels are often in error by 10%, it also is true that this potential error leads to a source of confusion in the identification of proteins from one lab to another. Thus, the specific details of a given protein purification are critical to the establishment of identity of a protein. In the case of UTAA, sufficient detail to reproduce the purification and identification of UTAA was not available until the later, more detailed publications. It is clear to me that the Euhus abstract was a preliminary report, presenting evidence that such an antigen may exist and may be isolated given sufficient work. Indeed, more convincing proof was established in later work.

Shively Declaration (Exhibit J). Thus, it again is submitted that there is overwhelming declaratory evidence that rebuts the examiner's position regarding the teachings of the Euhus *et al.* abstract. The reference is nothing more than an invitation to the skilled artisan to try to isolate an largely uncharacterized antigen. Without more, this abstract cannot be considered to provide the essential "enabling methodologies" or the "reasonable likelihood of success" that are required for a *prima facie* case of obviousness. *Paperless Accounting Inc. v. Bay Area Rapid Transit Sys.; In re O'Farrell*.

5. Individual Teachings of the Secondary References

Moving on the teachings of the individual references, one can easily dismiss the significance of Ljunquist, Goldenberg and the Pharmacia disclosure. Again, it is not contested that proteins can be isolated, nor is it argued that antibodies cannot be produced against many purified antigens. Similarly, appellants do not argue that ion exchange chromatography or gel filtration themselves are inoperable. These teachings, however, do not provide any indication as to how these procedures should be applied to the present invention, and as such, contribute little to the body of knowledge that would place the claimed invention within the grasp of the public. They merely constitute generally related background methodologies that are as relevant to the present invention as they are two thousands of similar, but unrelated inventions.

The only disclosures that bear upon UTAA are the sketchy teachings of Rote and Finck which, as far as the action is concerned, only establish that the described antigens are heat stable to 100°C, a fact that can hardly be said to remedy the problems outlined above with respect to reproducibility. Again, none of these references provides an enabling disclosure regarding the

structure of UTAA or how it should be isolated. In addition, it must be emphasized that the claims are drawn to a unique tumor antigen composition, not to methods by which such an antigen hypothetically could be produced. *In re Thorpe*, 227 USPQ 964, 966 (Fed. Cir. 1985) (“Patentability of a product does not depend on its method of production.”).

In light of the declarations of record, and the considerable discussion of why the rejection is improper, appellants respectfully submit that the record contains overwhelming evidence that the Euhus *et al.* reference is not enabling, nor does any other art being advanced remedy the deficiencies of the primary reference. Therefore, reversal of the rejection is respectfully requested.

6. Claims 63, 64, 66, 69 and 70 are Separately Patentable ?

Claims 63, 64, 66, 69 and 70 are drawn to various levels of UTAA purity. For example, claims 63 and 66 discuss “-fold” purification over UTAA found in urine, claim 64 discusses the percent total protein of UTAA, while claims 69 and 70 refer to a percent absence of immunoglobulin.

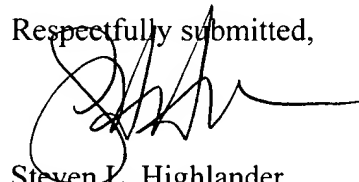
The examiner has simply glossed over these limitations in the claims in arguing that one would “expect,” in view of the similar treatment of UTAA by Euhus and applicants, that the values were achieved. This is improper. The examiner is, in essence, arguing inherency. It is well established that inherency has no place in an obviousness analysis. *In re Spormann*, 150 USPQ 449, 452 (CCPA 1966) (“Obviousness cannot be predicated on what is unknown”). Moreover, inherency also requires certainty, not probabilities. *Ex parte McQueen*, 123 USPQ 37 (Bd. App. 1958).

In fact, the only attempt made by the examiner to address these claims is to say that since Euhus reports that the sample was IgM and IgG free, then the 95% and 99.5% limitations are met. However, Euhus reports nothing regarding *other* immunoglobulin species – there could have been 1-6% contamination with other Ig's. In short, these significant additional elements of the claims are, in no way, addressed by the references, nor are they addressed by the examiner. For these reasons, appellants respectfully submit that claims 63, 64, 66, 69 and 70 are separately patentable over the art of record. ✓

X. CONCLUSION

It is respectfully submitted, in light of the above, all pending claims are non-obvious over the cited references. Therefore, appellants request that the Board overturn the pending grounds for rejection.

Respectfully submitted,



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APPENDIX 1 -- PENDING CLAIMS

19. A method for inducing or enhancing in a subject the production of antibodies reactive with UTAA comprising administering an effective amount of the antigen composition of claim 62.

62. An antigen composition comprising a substantially purified tumor antigen, wherein the tumor antigen is identified as comprising Urinary Tumor Associated Antigen (UTAA) subunit which, after reduction by β -mercaptoethanol and separation by SDS-polyacrylamide gel electrophoresis, exhibits a molecular weight of about 90 to 100 kD, and wherein said subunit contains glycosidase-sensitive carbohydrates, is heat stable at 100°C, and has an isoelectric point of about 6.1.

63. The antigen composition according to claim 62, wherein UTAA is purified at least about 100-fold over UTAA found in urine.

64. The antigen composition according to claim 62, wherein said UTAA is present as at least about 0.6% of total protein in said composition.

65. The method of claim 19, wherein said method comprises enhancing in a subject the production of antibodies reactive with UTAA.

66. The composition of claim 63, wherein said UTAA is purified 105-fold over UTAA found in urine.

69. The composition of claim 62, wherein said UTAA is about 95% free of (immunoglobulin) IgG.

70. The composition of claim 62, wherein said UTAA is about 99.5% free of (immunoglobulin) IgG.

72. The method of claim 65, wherein the observed enhancement of antibody production is about 2- to 5-fold.

73. A pharmaceutical composition comprising (i) an antigen composition comprising a substantially purified tumor antigen, wherein the tumor antigen is identified as comprising Urinary Tumor Associated Antigen (UTAA) subunit which, after reduction by β -mercaptoethanol and separation by SDS-polyacrylamide gel electrophoresis, exhibits a molecular weight of about 90 to 100 kD and (ii) a pharmaceutical buffer.

74. The pharmaceutical composition of claim 73, wherein said antigen composition is present as at least about 0.63 μ g/ml of buffer.

75. The pharmaceutical composition of claim 74, wherein said antigen composition is present as at least about 1.4 μ g/ml of buffer.

76. The pharmaceutical composition of claim 75, wherein said antigen composition is present as at least about 36 µg/ml of buffer.

77. The pharmaceutical composition of claim 76, wherein said antigen composition is present as at least about 40 µg/ml of buffer.

78. The pharmaceutical composition of claim 77, wherein said antigen composition is present as at least about 100 µg/ml of buffer.

79. The pharmaceutical composition of claim 78, wherein said antigen composition is present as at least about 200 µg/ml of buffer.

APPENDIX 2 -- EXHIBITS